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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/763,393	01/26/2004	Richard L. Veech	604-707	4584

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EXAMINER	
THOMAS, TIMOTHY P	
ART UNIT	PAPER NUMBER
1628	
MAIL DATE	DELIVERY MODE
02/22/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/763,393	VEECH, RICHARD L.	
	Examiner	Art Unit	
	TIMOTHY P. THOMAS	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35,37 and 38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35,37 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/12/2011*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/12/2011 has been entered.

Response to Arguments

2. Applicants' arguments, filed 1/12/2011, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

3. Applicant's arguments, see p. 7, filed 1/12/2011, with respect to the rejection under 35 USC 112, 2nd paragraph have been fully considered and are persuasive. The rejection of claims 35-39 has been withdrawn.

It is noted that the PDR for Nutritional Supplements reference supplied is not legible, and accordingly has not been considered on the IDS filed 1/12/2011. However, the American Journal of Clinical Nutrition reference establishes the meaning argued by applicant for the language retained in the claim. Based on this persuasive argument with the established meaning in the art, the rejection is withdrawn.

4. Applicant's arguments, see p. 7, filed 1/12/2011, with respect to the written description rejection have been fully considered and are persuasive. The rejection of claim 36 has been withdrawn.

5. Applicant's arguments, see p. 8, filed 1/12/2011, with respect to the rejection of claims 35-39 as anticipated by Martin and claim 36 as anticipated by Veech have been fully considered and are persuasive. The rejections of claims 35-39 and of claim 36 have been withdrawn.

The claim limitations for the amended claims were verified to be disclosed in at least the priority document PCT/US98/05072, as published in WO 98/41201 A1. Since this application predates the Martin and Veech references, the references are no longer applicable as prior art references. Accordingly, the rejections have been withdrawn.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

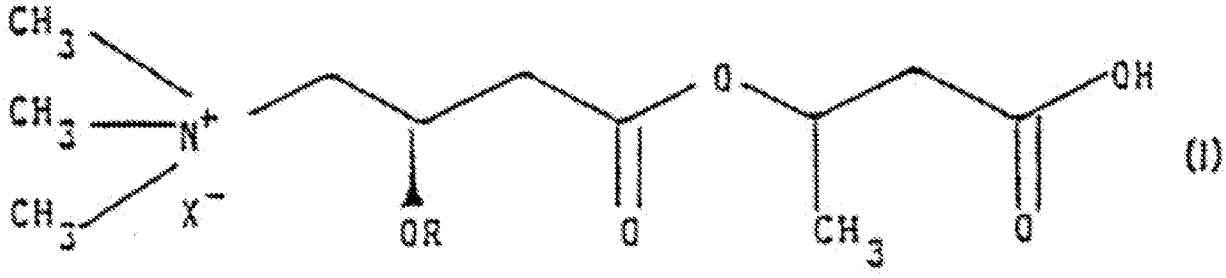
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. Claims 35 and 37-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tinti et al. (EP 0 443 996 A1; 1991; IDS 6/18/2010 reference); in view of Salvioli et al. ("L-acetylcarnitine treatment of mental decline in the elderly"; 1994; Drugs Under Experimental and Clinical Research; 20(4): 169-76; PubMed abstract; PMID: 7813389); and Bach et al. ("Medium-chain triglycerides: an update"; 1982; Am. J. Clin. Nutri. 36:950-962; IDS reference 1/12/2011).

Tinti teaches esters of beta-hydroxybutyric acid and pharmaceutical compositions containing them for inhibiting neuronal degeneration (title, abstract); compounds of formula (I) have the structure (abstract; para. 0001):



(I)

; these compounds are active in inhibiting neuronal degeneration as it occurs in Alzheimer's senile dementia (paragraph 0002); doses of the compounds in ranges from 5 or 15 to 500 mg in phials or tablets are administered (paragraph 0067); preferred dosages of 10-50 mg/kg , larger doses can be safely administered in view of the low toxicity of the compounds of the invention (10-50 mg/kg corresponds to 700-3500 mg administered to a 70-kg adult; paragraph 0066).

The compounds of formula (I) taught by Tinti, which are esters of beta-hydroxybutyric acid (a mixture of both D and L isomers) would be metabolic precursors

of D-β-hydroxybutyric acid and acetoacetate; they are also metabolic precursors of carnitine; the ester moiety would be expected to be hydrolysed *in vivo* resulting in the required elevation of the patient's ketone bodies. Esters of D-β-hydroxybutyric acid are specifically indicated to be useful in the instant invention (see instant specification, p. 20, lines 7-31), although esters recited in the claims are limited to no longer include esters containing carnitine. Concerning the beta-hydroxybutyric acid esters taught by Tinti, absent evidence to the contrary, hydrolysis of the ester bond would result in the required elevation of blood levels of D-β-hydroxybutyric acid and acetoacetate. Although Tinti is silent about levels of D-β-hydroxybutyric acid and acetoacetate achieved by the compounds taught, at the highest doses, it would be expected that (at some time point) the blood level would achieve an elevated concentration within the required elevated concentration range of 0.3mM to 20 mM, i.e., satisfying this requirement of the instant claims.

Tinti does not teach a compound within the scope of the administered compounds, such as D-β-hydroxybutyric acid, acetoacetate or medium chain length triglycerides. Additionally, neuronal degeneration and Alzheimer's senile dementia taught by Tinti would be a generic group of conditions/diseases (neuronal degeneration) and a generic group of characteristics within Alzheimer's senile dementia, that include the recited memory loss associated with aging, or memory loss caused by Alzheimer's disease, but memory loss associated with aging and memory loss associated with aging, caused by Alzheimer's disease are conditions obvious over, but not specifically named by Tinti.

Salvioli teaches a single-blind clinical trial carried out on 481 elderly subjects, with L-acetylcarnitine (LAC) administered 1500mg/day for 90 days; evaluation of drug efficacy included specific cognitive performances; LAC treatment improved the memory index, which had significant increase, with a favorable effect persisting after discontinuation of LAC; the conclusion reached upon statistical analysis of the data is that mild mental impairment in the elderly showed a significant improvement of several performances during and after treatment, and that other reports indicate that this drug may be effective in the treatment of dementia. Salvioli establishes that LAC at substantial doses (comparable to doses of the instant disclosed compounds, resulting in the blood level of ketone bodies in the range of the instant claims) have a measured benefit in memory loss associated with aging.

Bach teaches medium-chain triglycerides (MCTs) were first introduced in 1950 for the treatment of disorders of lipid absorption; since then a great deal has been learned about the metabolism and clinical use of MCTs and of their fatty acids (p. 950, 1st paragraph); MCTs are made up of a mixture of medium-chain fatty acids (MCFAs) (p. 950, 3rd paragraph); Figure 2, reproduced here (p. 952):

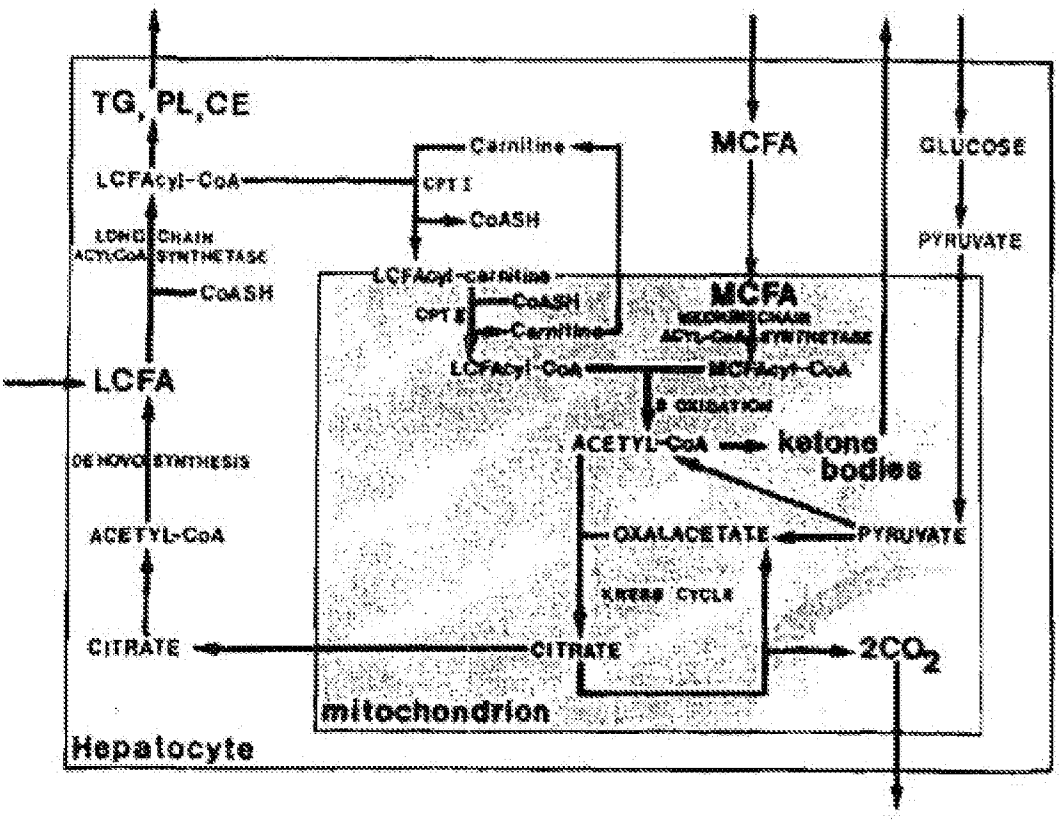


FIG. 2. Hepatic metabolism of fatty acids. *TG*, triacylglycerols; *PL*, phospholipids; *CE*, esterified cholesterol; CPT, carnitine palmityl transferase.

shows that MCFAs cross the double mitochondrial membrane, are acylated by an octanoyl-CoA synthase; the acyl-CoAs undergo β-oxidation, with production of acetyl-CoA (p. 952, last two paragraphs); excess acetyl-CoA follows various metabolic pathways, including ketogenesis (p. 953, 1st paragraph); MCTs are ketogenic, increasing the ketone bodies, although MCTs and oxaloacetic acid donors noticeably reduces the production of ketone bodies (p. 953, 3rd paragraph). MCTs, when supplied in the diet are rapidly oxidized, rendering many ketone bodies and supplying a quick source of energy, delivered to the whole body; all the extrahepatic tissues can use the ketone bodies supplied by the blood; when the blood level of β-hydroxybutyrate and

acetoacetate increases, the utilization of ketone bodies is enhanced (p. 954, last paragraph).

Bach further teaches applications of MCTs include deficiency of the carnitine system (p. 956, right); that patients suffering from a deficiency of muscular carnitine have been treated rather successfully with an MCT-based diet; in some cases carnitine was added, although the disorders observed in patients with carnitine palmityl transferase deficiency did not always regress when treated with a diet providing MCTs; that the more or less marked success of treatment with MCTs is probably due to the fact that only a small amount of MCFAs reach the muscle (p. 956, right, 3rd paragraph).

When the references are taken in combination, the teaching of Salvioli that LAC provides a therapeutic benefit in memory loss associated with aging, when considered with Figure 2 of Bach leads to the recognition that increased levels of ketone bodies is one expected result of substantial dosed amounts of LAC, such as the 1500 mg/day dosage of LAC taught in this reference; i.e., one of skill in the art would consider the potential mechanism of increased ketone bodies (e.g., increased levels of β-hydroxybutyrate and acetoacetate) to be responsible for the beneficial effect observed in the memory improvement. This putative mechanism that the Salvioli therapy involves increased levels of ketone bodies is further supported by the teaching that the Tinti compounds provide therapeutic benefit in inhibiting neuronal degeneration as it occurs in Alzheimer's senile dementia. Increase in the levels of ketone bodies would be expected for the Tinti compounds after hydrolysis of the esters; these compounds would directly result in increased levels of either of β-hydroxybutyrate and acetoacetate,

depending on the specific compound utilized; increasing levels of carnitine and/or LAC would also be expected. Considering that one of the metabolic products of carnitine and LAC is increased levels of ketone bodies, according to Figure 2 of Bach, would lead one of skill in the art to expect increased ketone bodies from each portion of the Tinti compounds to occur, and increased ketone bodies is likely the responsible mechanism for the beneficial result in Alzheimer's dementia taught by Tinti.

Based on the teaching of Bach that MCTs also result in increased ketone bodies, coupled with the teaching the MCTs often are acceptable substitutes for carnitine deficiency leads to a reasonable expectation that MCT therapy, at levels that substantially raise the level of blood ketones, will be a suitable substitute for the Tinti compounds and for LAC in the therapeutic applications taught by Tinti and Salvioli; i.e., leads to a reasonable expectation that MCT therapy would have been expected to benefit memory loss associated with aging and therapy for memory loss, as a part of Alzheimer's dementia.

Therefore, it would have been obvious to one of ordinary skill in the art to utilize medium chain triglycerides, at levels typically used in the ketogenic diet, in therapy of memory loss associated with aging and therapy for memory loss, as a part of Alzheimer's dementia, giving the methods of the instant claims. The motivation would have been a reasonable expectation that ketogenesis is responsible for the taught therapy in memory improvement of the aged individuals taught by Salvioli and in Alzheimer's dementia taught by Tinti. Additionally the motivation would have been the substitution of one art-recognized equivalent (medium chain length triglycerides,

resulting in increased levels of ketone bodies) for other art recognized equivalent compounds (the Tinti compounds and LAC, that reasonably are expected to result in increased ketone bodies levels).

With respect to the recited levels of blood ketones, similar amounts of MCTs as are taught by Tinti, at least at the highest levels, and of the amount of LAC dosed, each would have been expected to increase the ketone body levels to those of the ketogenic diet, i.e., to the recited range. Additionally, dosing MCTs in amounts that achieve the recited blood levels would have been obvious based on routine optimization of conditions. As pointed out in MPEP 2144.05 II, generally differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

It is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph).

Conclusion

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY P. THOMAS whose telephone number is (571)272-8994. The examiner can normally be reached on Monday-Thursday 6:30 a.m. - 5:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on (571) 272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Timothy P Thomas/
Primary Examiner, Art Unit 1628